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Tacrine and rate of progression in Alzheimer's disease – relation to ApoE allele genotype

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Summary. Today, cognitive impairment can be successfully treated with acetylcholine esterase inhibitors (AChE-I) in many, but not all, patients with Alzheimer's disease (AD). To investigate the relation between tacrine treatment, inheritance of ApoE ε4 alleles, and rate of progression, the differences in MMSE and CIBIC scores (efficacy parameters) after 6 and 12 months of tacrine (an AChE-I) treatment were investigated in 145 AD patients. Of these, 84 were ApoE ε4-positive (ApoE4) and 61 were ApoE ε4-negative (ApoE2-3). No differences were found after 6 months of treatment, but after 12 months the CIBIC scores revealed that the ApoE4 patients had declined more than the ApoE2-3 patients ($p < 0.05$). No differences were found for the last 6 months of treatment. The results primarily suggest a faster rate of decline in the ApoE4 AD compared to the ApoE2-3, but may also reflect that ApoE ε4 genotype inheritance is a negative predictor of treatment effect of tacrine in AD patients.

Keywords: Acetylcholine esterase, ApoE, Alzheimer's disease, CIBIC, MMSE, tacrine, treatment.

Introduction

The major cause of progressive cognitive decline in the world today is Alzheimer's disease (AD). Several million people globally are affected by AD and the proportion of affected individuals increases with the increasing elderly population. Several risk factors for AD have been identified, age being the strongest. Another established risk factor for AD is ApoE4 (Roses, 1996). An increased prevalence of the ApoE ε4 allele in the AD population has been found in several studies (for a review see Roses, 1996). Inheritance of ApoE ε4 alleles seems to bring about onset of AD at a lower than normal age in a dose-dependent manner (Corder et al., 1993). The pathophysiological changes associated with inheritance of ApoE ε4 in AD have not been fully elucidated, but have been suggested to be attributable to decreased activity in the cholinergic system (Allen et al., 1997; Poirier et al., 1995). However, some other studies have found no relation between ApoE ε4 and the cholinergic system (Anderson and Higgins, 1997; Corey-Bloom et al., 2000).

During the 1990s, treatment of cognitive impairment was made possible through the introduction of acetylcholine esterase inhibitors (AChE-I). Although the treatment with AChE-I is thought to be symptomatic, there are some indications that it may affect the course of the disease and extend the time to institutionalisation (Henke and Burchmore, 1997; Knopman et al., 1996; Smith et al., 1996). Many patients have shown marked improvement in cognitive functioning (Burns et al., 1999; Corey-Bloom et al., 1998; Minthon et al., 1993; Rosler et al., 1999). However, not all AD patients benefit from treatment with AChE-I. At least one-third of treated individuals experience no effect at all (Burns et al., 1999; Corey-Bloom et al., 1998; Minthon et al., 1993; Rosler et al., 1999). To ascertain who will benefit from treatment with AChE-I must be an important task for researchers. Some previous studies have indicated that the inheritance of ApoE ε4 alleles is a negative predictor for treatment effect, at least after up to 30 weeks of treatment (Farlow et al., 1996; Poirier et al., 1995; Schneider and Farlow, 1997).

The purpose of the present study was to investigate the relation between rate of decline and ApoE ε4 allele inheritance in AD patients treated with tacrine.

Material and methods

Subjects

Included in the study were 145 patients with AD. They had all received between 11 and 14 months of tacrine treatment. Their characteristics are summarised in Table 1.

All patients included in the study had been diagnosed with AD according to the NINCDS-ADRDA criteria (McKhann et al., 1984). Excluded were patients with unspecified dementia, mixed dementia, other forms of primary degenerative dementia (e.g. frontotemporal dementia), vascular dementia, severe psychiatric disease (e.g. schizophrenia), chronic alcoholism, distinct nondegenerative neurological disease (e.g. normotensive hydrocephalus), a history of severe head injury, severe infections in the

Table 1. Clinical characteristics

Diagnosis	N	Gender (M:F)	Age (y; Mean ± SD)	Duration dementia (y; Mean ± SD)	Degree of dementia (MMSE score; Mean ± SD)	MMSE range
All AD	145	61:84	70 ± 9.2	3.6 ± 2.4	21.2 ± 4.8	5–30*
ApoE ε4	84	41:43	69.8 ± 8.8	3.5 ± 2.5	20.6 ± 5.0	5–30
ApoE ε2-3	61	28:33	70.6 ± 9.9	3.8 ± 2.3	22.1 ± 4.4	9–30

All the values are expressed as means ± SD. The following abbreviations are used: *ApoE ε4* ApoE ε4 allele-positive AD patients, *ApoE ε2-3* ApoE ε4 allele-negative AD patients, *AD* Alzheimer's disease, *N* number of individuals; *M* male; *F* female, *y* years
*Some patients were rated as having AD although the MMSE score was 30

CNS or systemic diseases (e.g. malignant tumours) or secondary causes (e.g. hypothyreosis) of dementia according to the Diagnostic and Statistical Manual of Mental Disorders, 3rd edn, revised (DSM-III-R) or biochemical criteria. Excluded were also patients with cerebral infarcts and/or lacunas. All included patients underwent a thorough clinical investigation, including medical history, a physical, neurological and psychiatric examination, screening laboratory tests of blood (relevant laboratory tests to exclude other causes of dementia e.g. hypothyroidism), ECG, chest X-ray, EEG and computerised tomography or magnetic resonance imaging of the brain.

The local Ethics Committees approved the study. All patients (and/or their next of kin) gave their informed consent to participation in the study, which was conducted in accordance with the provisions of the Helsinki Declaration.

Cognitive assessments

The following psychometric scales were used as efficacy measures: the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and the Clinician's Interview-Based Impression of Change (CIBIC) (Knopman et al., 1994). The differences in MMSE score between the baseline rating and the ratings at 6 and 12 months, as well as the CIBIC scores at 6 and 12 months, were used as efficacy parameters. The differences in MMSE scores between the ratings after 6 and 12 months of treatment were also investigated. Not all patients underwent all cognitive tests at all times of investigation but all 154 underwent CIBIC at closure. At baseline, 148 underwent MMSE. At 5–7 months, 125 underwent MMSE and 150 CIBIC. At closure (11–14 months), 121 underwent MMSE and 154 CIBIC.

The MMSE is a rating instrument for cognitive functions in dementia. The score obtained is a measure of cognitive capacity; a score of 30 denotes absence of obvious cognitive defects and a score of 0 denotes severe cognitive impairment (Folstein et al., 1975).

The CIBIC was used after 6 and 12 months of treatment. It refers to the clinician's impression of change, which is rated as follows: 1 marked improvement, 2 moderate improvement, 3 mild improvement, 4 no change, 5 mild deterioration, 6 moderate deterioration and 7 marked deterioration (Knopman et al., 1994).

Determination of ApoE isoforms

Depending on the sample material available, determination of ApoE isoforms was performed either by isoelectric focusing (IEF) and Western blotting (Landen et al., 1996;

Skoog et al., 1997) or by polymerase chain reaction (PCR) and reverse DNA hybridisation using the Innolipa ApoE kit [Innogenetics, Ghent, Belgium].

Statistical analysis

As the efficacy parameters were not normally distributed and the variances were unequal in the two groups (ApoE4 versus ApoE2-3), nonparametric statistics were used for group comparisons. Mann-Whitney's U-test was used for comparisons between groups. Whenever relevant, adjustments for multiple comparisons were made. Pearson's Chi-square test was used for comparisons of ApoE ε4 allele frequency between the groups. Spearman's Rank Correlation test was used for calculation of correlations.

Results

Eighty-four patients were ApoE ε4-positive (ApoE4) and 61 were ApoE ε4-negative (ApoE2-3). There were no significant differences in the dosage of tacrine between the ApoE4 and ApoE2-3 groups at 6 or 12 months. Neither were there any significant differences between the two groups regarding gender, MMSE score, age or duration of disease at the start of the study.

No difference in treatment effect was seen with the MMSE after 6 or 12 months of treatment compared to baseline when comparing the ApoE2-3 AD patients with the ApoE4 AD patients (Fig. 1). Furthermore, no difference in effect, as measured by the MMSE, was found during the last 6 months. A significantly greater treatment effect in the ApoE2-3 AD patients was revealed by the CIBIC after 12 months of tacrine treatment ($p = 0.02$) (Fig. 2). No difference in effect, as measured by the CIBIC score at 6 months or for the change in CIBIC score during the last 6 months was found.

No correleations were found between the effect parameters (MMSE differences at 6 and 12 months and CIBIC scores at 6 and 12 months) and age, duration of disease, initial MMSE score or tacrine dosage either at 6 or 12 months.

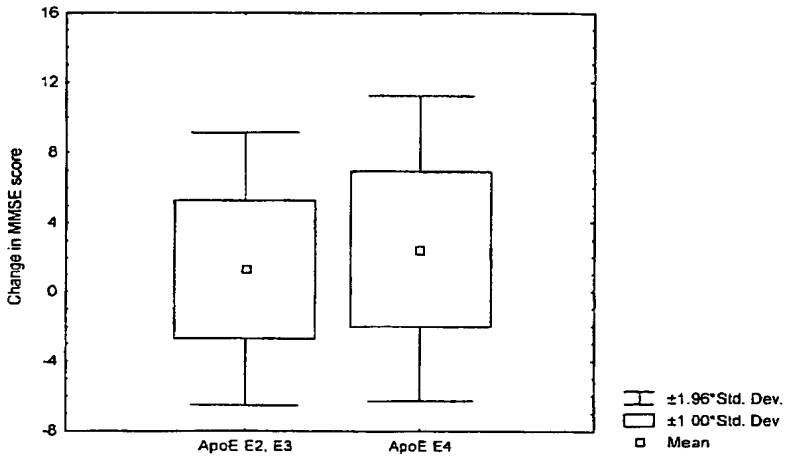

Fig. 1. Change from baseline in MMSE scores after 12 months of tacrine treatment in ApoE ε4 allele-negative (ApoE E2, E3) and ApoE ε4 allele-positive (ApoE E4) patients

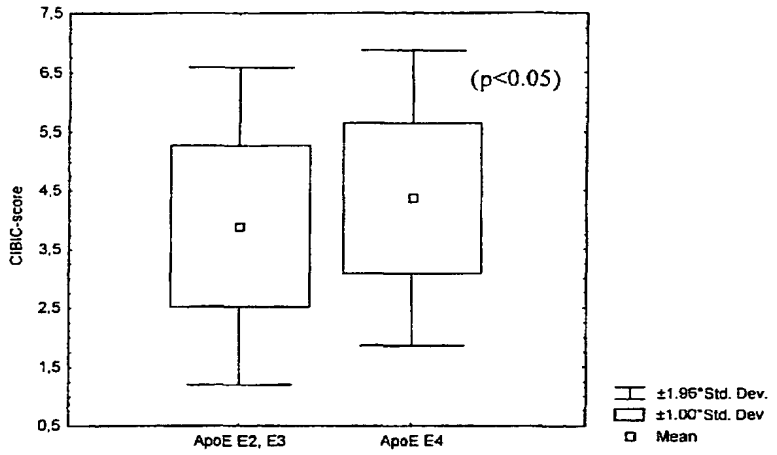

Fig. 2. CIBIC scores after 12 months of tacrine treatment in ApoE ε4 allele-negative (ApoE E2, E3) and ApoE ε4 allele-positive (ApoE E4) patients

Discussion

Increasing knowledge of predictors of treatment outcome is important for a number of reasons. First, and probably most important is the fact that it will enable doctors to prescribe a treatment that is likely to be effective; second, it will bring about an increasing understanding of why a treatment is effective; third, it may increase our knowledge of the underlying pathophysiological mechanisms and heterogeneity of AD; and fourth, it will increase the cost efficacy. Previous studies have suggested that ApoE2-3 AD patients benefit more than ApoE4 AD patients from treatment with AChE-I (Farlow et al., 1996, 1998; Poirier et al., 1995; Schneider and Farlow, 1997). The results of the present study may support this notion as it shows a relation between tacrine treatment, and a slower rate of decline in ApoE2-3 AD patients. In addition, the present study has followed the treated patients for a longer time. An influencing factor is the true rate of decline in these patients, which was not possible to correct for in the present study and which may have been faster in the ApoE4 AD patients (Craft et al., 1998). The effect of other influencing factors such as gender or the dosage of tacrine, which some previous studies have found to influence the effect of AChE-I treatment (Farlow et al., 1996; Knapp et al., 1994) was ruled out in the present study. Furthermore, we found no relation to duration or degree of dementia.

ApoE4 AD patients may have a more pronounced degeneration of cholinergic neurons (Allen et al., 1997). In AD patients studied by Poirier et al. (1995), the residual cerebral choline acetyltransferase (ChAT) activity and nicotinic binding sites in both the hippocampal formation and temporal cortex were decreased in ApoE4 patients but normal in ApoE2-3 patients. Thus, ApoE ε4 allele inheritance seems to be associated with reduced cholinergic activity in AD patients. This reduced cholinergic activity may affect the

outcome of treatment with AChE-I or possibly the rate of decline or both. Some previous studies have shown that AD patients have a reduced number of AChE-positive neurons (Etienne et al., 1986a,b), as well as a reduction of cerebral ChAT activity (Poirier et al., 1995). The finding that ApoE ε4 inheritance influences cholinergic activity in AD patients suggests a particular pathophysiological role for ApoE. It acts as a ligand in receptor-mediated internalisation of lipoproteins (Mahley and Innerarity, 1983). ApoE is also involved in the mobilisation and redistribution of cholesterol and phospholipid during the membrane remodelling associated with synaptic plasticity (Poirier et al., 1991, 1993). One study found that ApoE knockout mice fail to show synaptic plasticity in response to lesions in the entorhinal cortex (Masliah et al., 1995). Together these results may imply a vulnerability of cholinergic neurons to lesion in ApoE4 AD patients. Furthermore, some studies have found that the cerebrospinal fluid concentration (CSF) of ApoE is decreased in AD patients (Blennow et al., 1994; Hesse et al., 2000) and that ApoE ε4 carriers show reduced ApoE levels in the hippocampus and cortex as compared to normal controls and ApoE2-3 AD patients (Bertrand et al., 1995). Thus it is possible that lowered ApoE levels in the brain and in the CSF of AD patients will lead to reduced transportation or homeostasis of lipids and other plasma membrane components, which consequently will constitute the ground for impaired synaptic plasticity (Poirier et al., 1995). How ApoE E4 allele inheritance influences this is unknown.

In this study, we were able to obtain CIBIC scores for all and MMSE scores for the majority of the included AD patients. It would have been an advantage to have the Alzheimer Disease Assessment scale – cognitive items (ADAS-cog) scores for the one-year follow-up of the patients in order to more extensively investigate the long-term effects on cognition in AD patients and the relation to the ApoE allele genotype. However, the fact that the CIBIC scores clearly showed a difference supports the differential effect of ApoE2-3 and ApoE4 on treatment outcome. The validity of this study is also strengthened by the fairly large sample size. Moreover, the CIBIC but not the MMSE was designed to measure changes in cognitive variables. Consequently, the MMSE may not be the most reliable instrument in detecting changes from baseline after treatment with AChE-I. No significant correlations were found between degree of dementia, duration and initial MMSE score and the effect parameters. Some previous studies have suggested that the moderate to severely demented patients' benefit more from treatment with AchE-I (Anand et al., 2000). This could not be supported by the results of the present study.

To conclude, this study supports the hypothesis that inheritance of ApoE ε4 alleles is associated with a faster rate of decline in AD. The tacrine treatment may have affected the results being more effective in ApoE2-3 AD patients.

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